

Expression of the L-Fucose Moiety on Infrainfundibular Follicular Keratinocytes of Terminal Follicles, Its Decreased Expression on Vellus and Indeterminate Follicles of Androgenetic Alopecia, and Re-Expression in Drug-Induced Hair Regrowth

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The distribution of various glycoprotein molecules on the surface of follicular keratinocytes was studied with a panel of lectins with specificity for various sugar moieties on biopsy specimens from both bald/balding scalp and normal occipital scalp, of 23 patients with androgenetic alopecia as well as on biopsies of normal forearm skin of four patients. The most significant differences between bald and normal scalp biopsy were noted with *Ulex europaeus* agglutinin I (UEA I). We noted an increased ($91.8\% \pm 3.1$; mean \pm SE) expression of UEA I binding sites on the infra-infundibular follicular keratinocytes in anagen terminal scalp hairs, compared to $28.5\% \pm 5.2$ in the indeterminate (anagen) hairs of balding scalps, and $23.2\% \pm 6.3$ in the anagen follicles of vellus forearm hairs. By contrast, the telogen hairs demonstrated minimal UEA I staining: $4.0\% \pm 0.8$, mean \pm SE in telogen scalp hairs, $1.8\% \pm 0.5$ in telogen hairs of balding scalps (0% in

completely bald scalps, in which all the hairs were in the telogen phase), and $1.9\% \pm 0.2$ in telogen forearm hairs. The percentage of UEA I staining correlated with the length of the infrainfundibular follicles in all cases studied. In three cases of hair regrowth after hair growth promoters, the UEA I staining increased to $80.6\% \pm 6.1$ in anagen hairs and correlated with increased length of infrainfundibular follicles. Our data indicate that there are 1) marked differences between anagen and telogen follicles in UEA I binding to infrainfundibular follicular keratinocytes; 2) the percentage of UEA I staining reflects the size (length) of the infrainfundibular hair follicle; and 3) the anagen follicles of balding scalps (indeterminate hairs) show UEA I staining resembling that exhibited by anagen follicles of vellus hairs. *J Invest Dermatol* 98:73–78, 1992

The carbohydrate moieties of cell-surface glycoproteins have been involved in cell-cell recognition [1,2], cellular proliferation [3–5], and differentiation [6–8]. In particular, the L-fucose moiety is a terminal constituent of many cell-surface glycoproteins in rapidly growing cells [3–5]. Lectins are molecules, usually found in plants, but also in animals, that have a marked affinity for these carbohydrate moieties on cell-surface glycoproteins. The lectin from the gorse plant, *Ulex europaeus* agglutinin I (UEA I), which avidly binds the L-fucose molecule, has been used to detect the presence of L-fucose on the oligosaccharide chains of cell-surface glycoproteins [9]. Increased expression of UEA I binding sites have been noted on keratinocytes undergoing terminal differentiation [10,11], and in conditions characterized by rapid epidermal turnover [12,13].

Although androgens [14] are felt to be responsible for androgenetic alopecia, the pathophysiology of this disease is currently unknown. However, it has been observed that the scalp in androgenetic alopecia is not “bald” but covered by a fine “fuzz” of vellus hairs [15,16] that fail to become terminal hairs. In this study, UEA I lectin was used in a study of 23 patients with androgenetic alopecia in the hope that the findings may shed some light on the growth and differentiation of vellus and indeterminate follicles of bald and balding scalp, as compared to those of normal controls.

PATIENTS AND METHODS

Patient Population Twenty-three patients with ages ranging from 28 to 72 years, mean 45 years, were studied. The patients, as classified according to Hamilton's classification [17], had androgenetic alopecia ranging in severity from type III to type VI. They were randomly assigned to the following treatment groups: a) minoxidil 0.5%; b) retinoic acid 0.05%; c) minoxidil 0.1% with retinoic acid 0.05%; and d) minoxidil 0.5% with retinoic acid 0.05%. The formulation used, provided by Gail Bazzano, Ph.D., used propylene glycol in a liquid preparation [18]. All the patients were initially subjected to punch biopsies of both the bald (frontal or vertex areas) and hairy, occipital (normal, uninvolved) scalp. The patients were followed up in the Dermatology Clinic, Veterans Administration Medical Center, Sepulveda, CA, every 3–6 months. Assessment was by clinical impression and photography, and only moderate terminal hair growth or better was rebiopsied. As this study was not

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Abbreviations:

- ABC: avidin-biotin complex
- OCT: optimum cutting temperature
- UEA I: *Ulex europaeus* agglutinin I

designed to test the efficacy of either minoxidil or retinoic acid, actual hair counts of vellus and terminal hairs were not done. Scalps of study patients were, however, assessed by light microscopy on biopsies. Vellus hairs from forearm biopsies of four patients also served as controls.

Scalp Biopsies Two punch biopsy specimens were taken from each of the bald and normal scalps from all 23 patients before therapy, and from the only three patients with areas of moderate hair regrowth (terminal hairs) after therapy; these latter biopsies were taken at 9 to 15 months after instituting therapy. Biopsies were also taken from treated bald areas that failed to grow hair in six patients. The biopsies were processed for light microscopy and lectin studies.

Light Microscopy Four-millimeter punch biopsies were fixed in 10% neutral buffered formalin and processed for light microscopy. Paraffin sections were stained with hematoxylin and eosin and examined under a Leitz light microscope.

Lectin Studies Adjacent 4-mm punch biopsy specimens were taken for lectin studies. These were embedded in OCT compound (Tissue tek), snap-frozen in liquid nitrogen, and stored at -70°C . Cryostat sections were placed on poly-L-lysine-coated slides, dried overnight at room temperature, fixed in acetone at room temperature for 10 min, and allowed to dry thoroughly. The sections were then incubated with various biotinylated lectins (Table I) from Vector Laboratories Inc. The resultant sections were then processed by using the Vectastain ABC kit, and were incubated with diaminobenzidine.

Criteria for Diagnosis of Anagen and Telogen Follicles Anagen follicles were those with the following characteristics on light microscopy: 1) the bulbar portions of the follicles were well developed; 2) the follicles contained well-developed hair shafts; 3) the infrainfundibular portions of the follicles were greater in length than the infundibular portions of the follicle (with the exception of an anagen follicle in the earliest budding phase shown in Fig 1a); and 4) there was no crimpling of the bulbar portions of the follicle as seen in early catagen.

Telogen follicles, on the other hand, had the following characteristics: 1) the bulbar portions of the follicles were small and underdeveloped; 2) there was frequently no hair within the follicle; 3) the infrainfundibular portions of the follicle were nearly always (with the exception of follicles in early telogen, which are recognized in turn by the crimped appearance of the bulbar epithelium) shorter in length than the infundibular follicle; and 4) presence of crimpling of the bulbar follicle denoting early telogen.

Indeterminate follicles were seen in balding scalp. These possessed features intermediate between terminal and vellus follicles, but more closely resembled the latter. The anagen phase of the intermediate follicles were smaller than the terminal follicles, with the smaller bulbar portions situated either above or below dermosubcutaneous junctions. The telogen phase of these follicles resembled their vellus counterpart.

Measurement of Length of Infrainfundibular Follicle Longitudinal sections of hair follicles were measured in paraffin sections stained with hematoxylin and eosin of all biopsies. We photographed the follicles at $40\times$ magnification, focusing on the infrainfundibular portions between the sebaceous duct/follicular junction and the hair bulb, using slightly overlapping photomicrographs.

These were printed out at a $2.5\times$ magnification. The length of the follicles between the sebaceous duct-follicle junction and the tip of the bulb was then measured, and the data were corrected for the magnification by dividing by 100.

Measurement of Percentage of UEA I-Positive Infrainfundibular Keratinocytes Longitudinal sections of the frozen biopsies processed for UEA lectin were measured for percentage of UEA I lectin binding by infrainfundibular follicular keratinocytes as follows. The lectin-stained sections were photographed at a magnification of $40\times$, and slightly overlapping photomicrographs were printed at a further magnification of $2.5\times$. The surface areas of UEA I-positive keratinocytes were then determined by means of a graphics tablet connected to a microcomputer, and their percentages calculated. Cross sections of the bulbar and suprabulbar areas of the follicles were also measured in some patients. The data devised from these sections were found not to differ significantly from those obtained from longitudinal sections.*

RESULTS

The distribution of the various glycoproteins characterized by identification of their sugar moieties, was studied by the use of a panel of lectins, with specificity for the various sugar moieties as shown in Table I. The most significant differences were noted with studies employing UEA I lectin. The results have been summarized in Figs 1-6.

Scalp Biopsies In biopsies from uninvolved (occipital) scalp, the UEA I lectin, which has L-fucose specificity, was observed to bind strongly to the surface plasma membrane of the infrainfundibular follicular keratinocytes ($91.8\% \pm 3.1$; mean \pm SE) of the anagen follicles (terminal hairs), from early anagen (Fig 1a), to the more established follicles of anagen hairs situated just above (Fig 1b) or below (Fig 1c) the dermosubcutaneous junction. However, in terminal hairs undergoing early catagen, recognized by the crimpling of the internal root sheath (Fig 1d), the follicular keratinocytes of the external root sheath were the first to lose the L-fucose moiety. This is demonstrated by loss of UEA I binding on follicular keratinocytes of the external root sheath (Fig 1e). This alteration in UEA I binding sites occurs prior to a decrease in perifollicular vascularity (Fig 1c). Well established telogen follicles of occipital scalp, however, showed minimal ($4.0\% \pm 0.8$) UEA I positivity (Fig 1e).

By contrast, in biopsies from completely bald scalps (20 of 23 patients), the only follicles present were telogen follicles, which showed no staining with UEA I lectin in their infrainfundibular portions. [There is usually variable UEA I positivity of the infundibular portions of the follicles in occipital, balding (indeterminate) and vellus forearm follicles]. Even the anagen follicles situated below the dermosubcutaneous junction (Fig 2a,b) in balding scalps revealed little and more incomplete binding (Fig 2a,b) of the infrainfundibular follicular keratinocyte epithelium to UEA I lectin than anagen-phase terminal hairs of occipital scalp (Fig 1b,c); the less affected scalps revealing more UEA I positivity than the more affected scalps. The telogen follicles of balding scalp showed little or no UEA I staining ($1.8\% \pm 0.5$).

In biopsies from areas of new hair regrowth (three patients) after treatment with hair-growth promoters, it was noted that UEA I lectin binding sites were increased ($80.6\% \pm 6.1$) in the anagen follicles, with the lectin binding strongly to the infrainfundibular follicular keratinocytes (Fig 3). This increase in UEA I binding was not observed in the six patients in whom visible hair regrowth was not noted by both patient and investigator. Telogen follicles in all patients showed minimal (Fig 6) UEA I positivity.

Vellus Follicles (Forearm) Biopsies In the vellus follicles of the forearm, the anagen hairs revealed decreased ($23.2\% \pm 6.3$) UEA I-positive (Fig 4a,b) infrainfundibular follicular keratino-

Table I. Lectins Used in This Study

Lectin	Source	Sugar Specificity	Dilution
Concanavalin A	Vector Labs	Glucose, mannose	1:40
Peanut agglutinin	Vector Labs	β -D-galactose	1:40
Ulex europaeus agglutinin I (UEA I)	Vector Labs	L-fucose	1:80
Wheat germ agglutinin	Vector Labs	N-acetyl-glucosamine (sialic acid)	1:400

* Heng MCY (unpublished data).

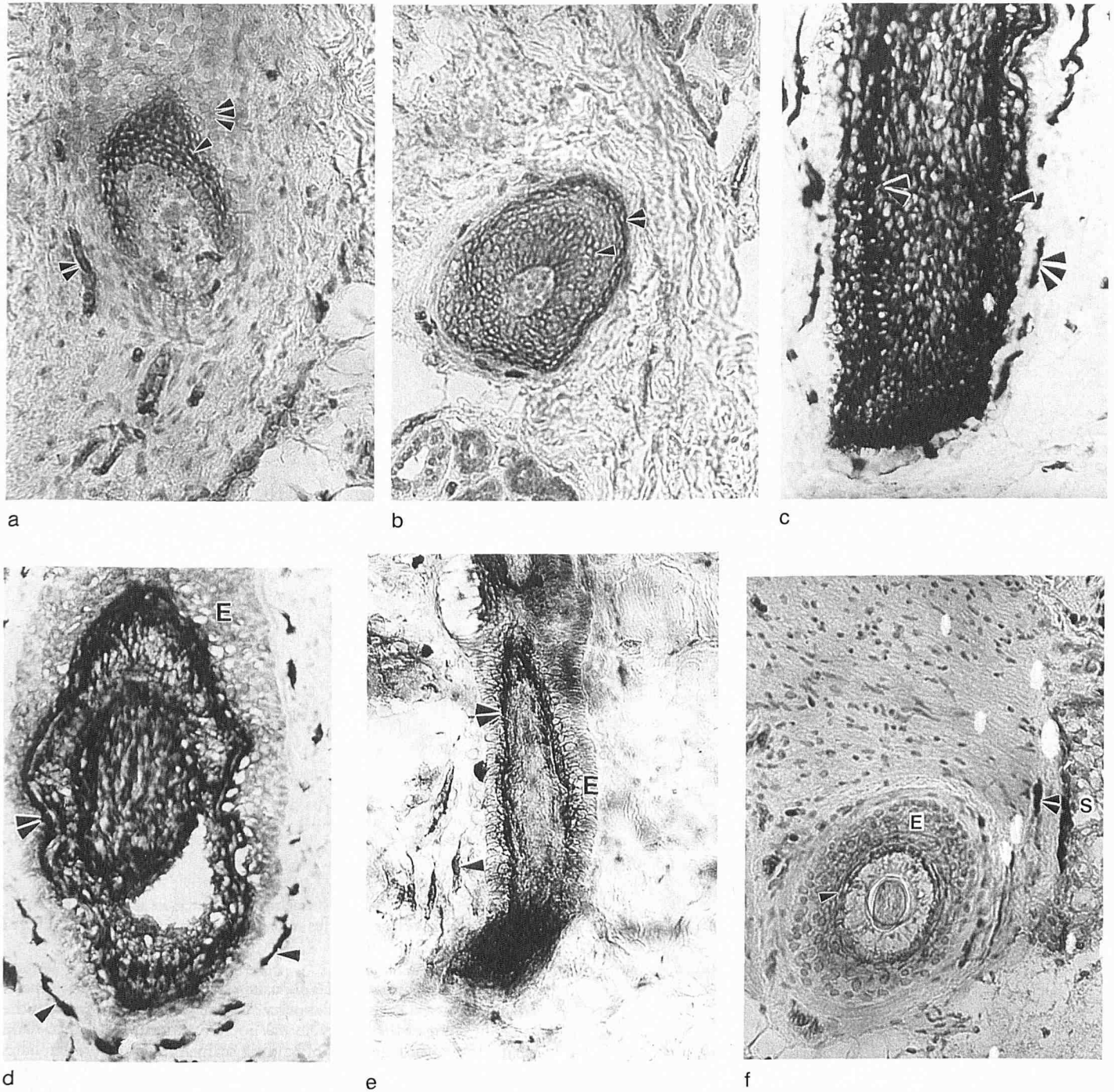


Figure 1. (a) Terminal hair occipital scalp follicle in early anagen, showing UEA I positivity of the bulbar follicular keratinocytes (single arrows) and perifollicular blood vessels (double arrows). Note negative UEA I binding of cells of the external root sheath (triple arrows). Magnification $\times 187.5$. (b) Terminal occipital follicle (oblique section through bulb) in a more advanced stage of anagen than (a), showing UEA I positivity of keratinocytes of both the external root sheath (double arrows) and internal root sheath (single arrow). Magnification $\times 187.5$. (c) Terminal occipital follicle (longitudinal section) in anagen phase, showing UEA I positivity of infrainfundibular keratinocytes of both the external (single arrow) and internal (double arrows) root sheath. Note the numerous perifollicular blood vessels (triple arrows). Magnification $\times 250$. (d) Terminal occipital follicle in early catagen, showing crimping of the internal root sheath that retains UEA I positivity (double arrows). Note the loss of UEA I positivity from the infrainfundibular follicular keratinocytes of the external root sheath (E). Note also presence of numerous perifollicular vessels (single arrows). Magnification $\times 250$. (e) Terminal occipital scalp follicle in late catagen/early telogen with a shriveled bulb, showing loss of UEA I positivity from the infrainfundibular keratinocytes of the external root sheath (E) and decreased staining of the internal root sheath (double arrows). Magnifications $\times 150$. (f) Terminal occipital scalp follicle in telogen situated at the level of the sebaceous glands (S). Note the presence of minimal UEA I positivity of the internal root sheath (single arrow) and essentially negative UEA I binding in the external root sheath (E). Blood vessels (double arrows) are UEA I positive. Magnification $\times 187.5$.

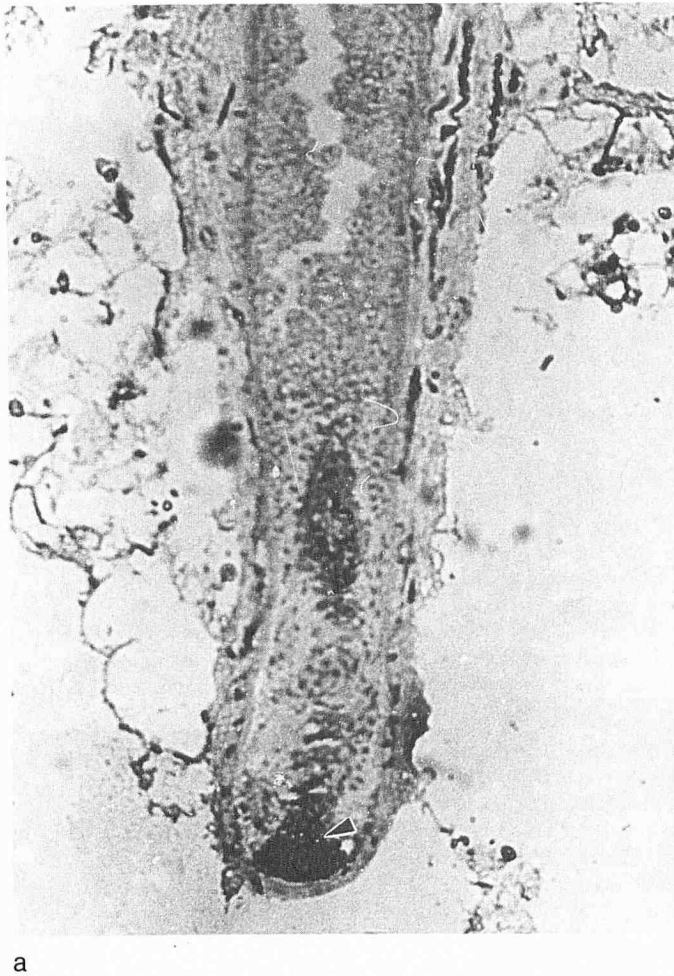


Figure 2. (a) Indeterminate anagen follicle (longitudinal section) from balding scalp showing minimal UEA I positivity (single arrow) of follicle situated below the dermosubcutaneous junction. Magnification $\times 250$. (b) Indeterminate anagen follicle (cross-section) from balding scalp showing some UEA I positivity of the internal root sheath (single arrows) and minimal or no staining (E) of the keratinocytes of the external root sheath (E). Magnification $\times 400$.



Figure 3. New hair regrowth (treated) anagen hair (oblique section) showing UEA I positivity of the infrainfundibular follicular keratinocytes of the external root sheath (E) and internal root sheath (I). Magnification $\times 250$.

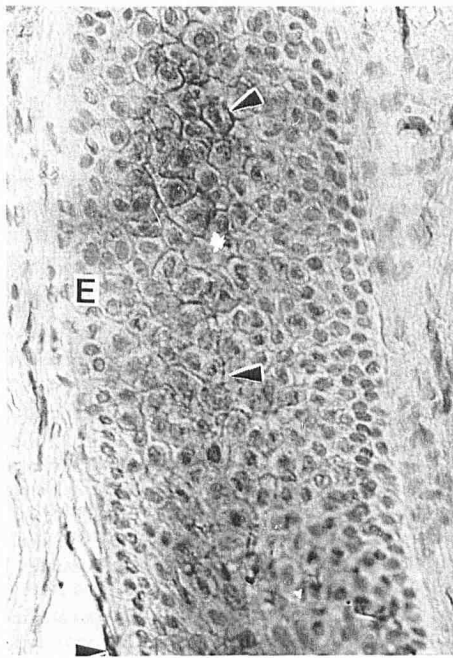
cytes, with much weaker staining than noted in the terminal follicles. Telogen vellus follicles revealed minimal ($1.9\% \pm 0.2$) UEA I positivity.

Correlation Between UEA Positivity and Hair Cycle A positive correlation between the percentage of UEA I positivity and the anagen phase of the hair cycle was noted for terminal occipital scalp hairs, indeterminate hairs of balding scalp and vellus forearm hairs (Fig 5). In addition, UEA I positivity of $91.8\% \pm 3.1$ in anagen-phase terminal hairs was significantly different ($p < 0.001$) from that of $28.5\% \pm 5.2$ in the anagen-phase hairs of balding scalps. On the other hand, there is no significant difference ($p > 0.05$) between the UEA I positivity of the balding scalp ($28.5\% \pm 5.2$) and vellus forearm hairs ($23.2\% \pm 6.3$; Fig 5). The UEA I positivity of the new hair regrowth after therapy with hair promoters tend to resemble that of terminal hairs rather than vellus hairs (Fig 5). However, as the numbers are too small, statistical significance was not assessed for this group.

Correlation Between Length of Infrainfundibular Follicle and Hair Cycle The length of the infrainfundibular follicles also correlated with the anagen phase of the hair cycle in all hair types (Fig 6), being much longer in the anagen than in the telogen follicles. Again the results were significantly different between the terminal hairs (3.4 ± 0.5 mm) of occipital scalp, and indeterminate hairs (1.7 ± 0.6 mm) of balding scalp ($p < 0.01$), but not significantly different ($p > 0.05$ mm) between the indeterminate hairs (1.7 ± 0.6 mm) and vellus hairs (1.5 ± 0.4 mm; Fig 6). In the three



a



b

Figure 4. (a) Vellus (forearm) anagen follicle (longitudinal section through the bulb) showing minimal UEA I positivity (single arrows) of both external (single arrows) and internal root sheath (double arrows). Note the weak UEA I staining compared to the blood vessels (triple arrows). Magnification $\times 400$. (b) Vellus (forearm) anagen follicle (suprabulbar portion) showing minimal UEA I positivity of follicular keratinocytes of the internal root sheath (single arrows), but no staining of the external root sheath (E). The weakness of the UEA I binding can be compared with UEA I positivity on perifollicular blood vessels (double arrows). Magnification $\times 400$.

patients with hair regrowth, there was an increase in the length of the infrainfundibular follicle (Fig 6). Statistical significance was not assessed due to the smallness of the sample.

DISCUSSION

Our data indicate marked differences between UEA I expression on infrainfundibular follicular keratinocytes of anagen versus telogen follicles in occipital scalp (terminal hairs), bald/balding scalp (indeterminate hairs), and forearm (vellus hairs) biopsy specimens. In addition, marked differences in the extent and degree of UEA I binding was observed between anagen follicles of terminal, indeterminate and vellus hairs.

The lectin-binding studies with UEA I lectin shows, in uninvolved scalp biopsy specimens, a correlation between UEA I binding

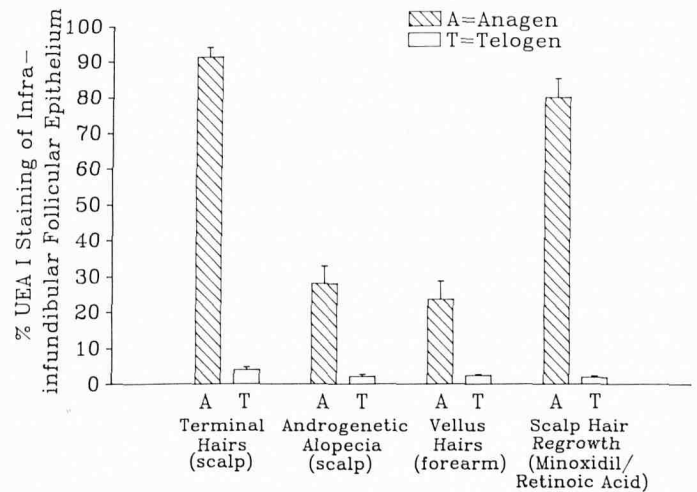


Figure 5. Comparison of the percent UEA I positivity of infrainfundibular follicular keratinocytes of terminal scalp, vellus (forearm), and balding follicles (untreated, and after new hair regrowth) in the anagen and telogen phase. Results are expressed as mean \pm SEM.

sites (L-fucose specificity) and the proliferative phase of the cell cycle, being maximal in the anagen phase of terminal follicles of occipital scalp, decreasing in the early catagen follicles, and minimal in catagen/telogen (Fig 1a-e). As the sugar moieties are found on the plasma membrane, the UEA I-positive reaction features dark staining, which outlines the plasma membrane of the follicular keratinocytes (Fig 1a,b). It thus appears that the density of the L-fucose lectin binding sites was noted to affect the infrainfundibular follicular keratinocytes of the external root sheath (Fig 1d) before any decrease in perifollicular vascularity was detected (Fig 1d). Furthermore, the loss of UEA I binding sites, noted to be minimal in early catagen (Fig 1d), was even more marked in late catagen/early telogen (Fig 1e) and late telogen in occipital (terminal) scalp follicles. decrease in perifollicular vascularity was detected (Fig 1d). Furthermore, the loss of UEA I binding sites, noted to be minimal in early catagen (Fig 1d), was even more marked in late catagen/early telogen (Fig 1e) and late telogen in occipital (terminal) scalp follicles. These findings suggest that UEA I positivity on infrainfundibular follicles may be a useful marker for the proliferative anagen phase of the hair cycle, particularly for terminal scalp hairs. The paucity of UEA I positivity on the infrainfundibular follicular keratinocytes in the anagen phase of indeterminate hairs from balding scalp (no

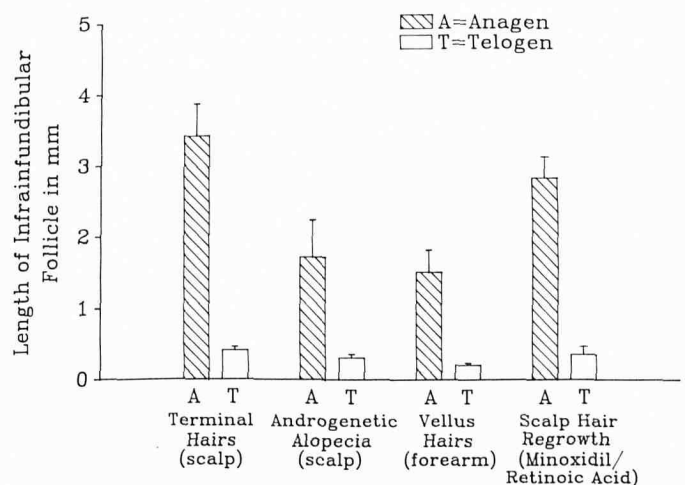


Figure 6. Comparison of the length of the infrainfundibular follicle in mm in terminal scalp, balding scalp (untreated and after new hair regrowth) and vellus forearm follicles. Results are expressed as mean \pm SEM.

anagen hairs were noted in the completely bald scalps) and vellus (forearm) hair suggests that UEA I positivity may also reflect the degree of proliferation in the different types of follicles, being maximal in the terminal hairs and minimal in the vellus forearm hairs. Although a few indeterminate anagen hairs in balding scalp were observed to express greater UEA I binding than vellus forearm hairs, suggesting perhaps that these were in transition between unaffected terminal scalp hairs and telogen/vellus hairs observed in bald scalps, the indeterminate follicles of balding scalp, when taken as a group, were no different from vellus forearm follicles in terms of UEA I binding characteristics. The data in Fig 6, which correlates the length of the infrainfundibular follicle with the anagen phase of the hair cycle, again focuses on the similarity between the growth patterns between the indeterminate follicles of androgenetic alopecia and vellus follicles (Fig 6).

The expression of L-fucose specific UEA I binding sites on keratinocytes has been used as a marker for terminally differentiated keratinocytes [10,11]. As increased UEA I binding sites have been reported in hyperproliferative disorders such as psoriasis [12,13], increased UEA I binding sites in both the anagen phase of terminal hairs and psoriasis may reflect an increased number of proliferating cells committed to terminal differentiation in these cases. In addition, it has been observed that the L-D galactose moiety expressed on basal and lower spinous keratinocytes is converted to the L-6-deoxygalactose (L-fucose) moiety on terminally differentiated keratinocytes by the action of glycosidases [19]. It may be inferred that the appearance of the L-fucose moiety on follicular keratinocytes is associated with loss of the L-D galactose moiety on basal and lower spinous keratinocytes. It is significant that the loss of the L-D galactose moiety from cell-surface glycoproteins has been shown to be associated with loss of contact inhibition [20]. Increased L-fucose specific UEA I binding sites on infrainfundibular follicular keratinocytes may, therefore, reflect increased proliferation of follicular keratinocytes resulting from loss of contact inhibition. The resultant increase in cell division in the anagen phase, as well as the length of time the follicles remain in the anagen phase may explain the differences in the length and size of both follicle and hair shaft in the different types of hair.

The enhanced expression of L-fucose specific UEA I binding sites (Fig 3) on infrainfundibular follicular keratinocytes in three patients with new hair regrowth due to minoxidil and/or retinoic acid appears to parallel proliferative changes induced in these follicles. Our data showing an increase in infrainfundibular follicular length in these newly differentiated hair follicles (Fig 6) appear also to support the above concepts.

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